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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,899	02/23/2004	Minoru Fujimori	2004_0290	5937

7590 11/26/2007
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EXAMINER

LONG, SCOTT

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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11/26/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/782,899

Applicant(s)

FUJIMORI ET AL.

Examiner

Scott D. Long

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 28 and 30-46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28, 30-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The examiner acknowledges receipt of IDS, Applicant's Remarks and Claim Amendments filed 8/6/2007.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/2007 has been entered.

Claim Status

Claims 28, 31-33 are amended. Claims 1-27 and 29 are canceled. Claims 28 and 30-46 are under current examination.

Priority

This application claims benefit as a Continuation of U.S. Application No. 09/816,391 filed 26 March 2001 (abandoned). The instant application also claims benefit from foreign application JAPAN 2000-287688 filed 12 September 2000. The

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applicant has submitted a certified English translation of foreign application (JAPAN 2000-287688). Consequently, the application has been granted the benefit date, 12 September 2000, from foreign application JAPAN 2000-287688.

Response to Claim Rejections - 35 USC § 112

Response to Claim Rejections - 35 USC § 112, second paragraph

The Applicant's arguments (Remarks, page 10) and claim amendments (filed 8/6/2007) regarding rejection of claim 32 under 35 USC 112, 2nd paragraph have been fully considered and are persuasive.

The claim amendments make the rejection moot, therefore, the examiner hereby withdraws the rejection of claim 32 under 35 USC 112, 2nd paragraph

Response to Claim Rejections - 35 USC § 112, first paragraph (written description)

The Applicant's arguments (Remarks, pages 10-11) and claim amendments (filed 8/6/2007) regarding rejection of claim 32 under 35 USC 112, 1st paragraph have been fully considered and are persuasive.

The claim amendments, removing the claim language, "derived from" make the rejection moot, therefore, the examiner hereby withdraws the rejection of claim 32 under 35 USC 112, 1st paragraph (written description).

Response to Claim Rejections - 35 USC § 112, first paragraph (written description)

The Applicant's arguments (Remarks, pages 5-8) and claim amendments (filed 8/6/2007) regarding rejection of claims 28 and 30-34 under 35 USC 112, 1st paragraph (written description) have been fully considered, and are persuasive.

The claim amendments to claim 28 have narrowed the scope of the genus of promoters to a genus sufficiently narrow, so that a skilled artisan can reasonably say that the applicant is in possession of the claimed genus of promoters. The working examples which utilize SEQ ID NO:1 are clearly representative species of promoter and terminator of the claimed genus. Furthermore, the applicant has provided references that indicate a strong evolutionary conservation among histone-like binding proteins found in the genus *Bifidobacterium*. Because the single working example is a clearly representative species of promoter from a well characterized genus, the examiner finds that the applicant has overcome the rejection.

Therefore, the examiner hereby withdraws the rejection of claims 28 and 30-34 under 35 USC 112, 1st paragraph (written description).

Response to Claim Rejections - 35 USC § 103

The Applicant's arguments (Remarks, pages 5-8) and claim amendments (filed 8/6/2007) regarding rejection of claims 28 and 30-46 under 35 USC 103 have been fully considered and are persuasive.

The applicant argues that limitations of the newly amended claim 28 are not taught by Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al. (US applic. 2003/0103952). The applicant concurs, that the newly amended limitations are not taught by the Yazawa in view of Brown.

Therefore, the examiner hereby withdraws the rejection of claims 28 and 30-34 under 35 USC 103.

NEW REJECTIONS

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 30-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the

application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement*; (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 28 is broadly drawn, such that it applies to a genus of transformed Bifidobacterium, comprising DNA encoding proteins with either an anti-tumor activity or that converts a precursor into an antitumor substance. However, the working examples (Example 3, pages 55-) provided in the instant application only demonstrate individual species of Bifidobacterium comprising antitumor (or precursor converting) genes, specifically Bifidobacterium longum comprising the gene for cytosine deaminase.

The genus Bifidobacterium comprises the following species: *B. adolescentis*, *B. angulatum*, *B. animalis*, *B. asteroides*, *B. bifidum*, *B. boum*, *B. breve*, *B. catenulatum*, *B. choerinum*, *B. coryneforme*, *B. cuniculi*, *B. denticolens*, *B. dentium*, *B. gallicum*, *B. gallinarum*, *B. indicum*, *B. infantis*, *B. inopinatum*, *B. lactis*, *B. longum*, *B. magnum*, *B. merycicum*, *B. minimum*, *B. pseudocatenulatum*, *B. pseudolongum*, *B. pullorum*, *B. ruminantium*, *B. saeculare*, *B. subtile*, *B. suis*, *B. thermacidophilum*, *B. thermophilum*.

The scope of the genes encompassed by the claims includes any DNA protein encoding a protein that has anti-tumor activity or converts a precursor into an antitumor

substance, including all allelic, polymorphic, and splice variants of these genes, including those isolated from any organism, including also mutated forms of these genes, wherein the claimed bacterium are transformed with these various genes.

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

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unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the potentially large number of Bifidobacterium comprising an enormous number of genes encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28 and 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al. (US applic. 2003/0103952) and further in view of Goshima et al. (Biochimie, 1990. vol.72: 207-214) and further in view of Natori et al. (Biochimie. Volume 70, Issue 12, December 1988, Pages 1765-1774).

Yazawa teaches using *Bifidobacterium longum* as a gene delivery vector for treating cancer in a buffer or solution, (that is, a pharmaceutical preparation). However, Yazawa does not specifically teach introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using *Bifidobacterium longum*.

However, at the time the invention was made, introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using a genetically modified bacterium was well known to one of ordinary skill in the art as exemplified by Brown (columns 1-26). Brown teaches using a genetically modified bacterium to deliver an enzyme to the

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hypoxic/necrotic environment of a tumor and systemically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme (columns 25-26). The enzyme/prodrug combination can be selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs (columns 5-6).

Neither Yazawa et al. nor Brown et al. teach utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes.

However, the HU promoter was known as in the art as a promoter which highly expresses HU protein in *Bifidobacterium longum* (Natori et al.; Goshima et al.). However, utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes was not performed by any other researchers at the time of the filing. The examiner still believes that it is obvious to use *Bifidobacterium longum* as a vehicle for delivery of cancer therapeutics.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown and Natori, namely to use a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in a method to treat tumor tissues under anaerobic conditions and further using the HU promoter to express the anti-tumor substances.

One of ordinary skill in the art would have been motivated to introduce the DNA encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into tumor tissues under anaerobic conditions using the genetically modified bacterium because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in an individual after systemic application and pro-drug cancer therapy was well known to one of ordinary skill in the art for treating tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, namely to use any enzyme/prodrug combination in the method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use an enzyme/prodrug combination selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs because the enzyme/prodrug combinations were well known to one of ordinary skill in the art for treating hypoxic tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Yazawa taken with Brown and Natori, namely to use an expression vector that has a HU promoter and terminator that function in a Bifidobacterium. One of ordinary skill in the art would have been motivated to use a histone-like binding protein promoter and terminator of Bifidobacterium because one of ordinary skill in the art understands that a promoter and

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a terminator are required for the vector to express the protein of interest. Furthermore, having a promoter which expresses an important protein such as those interacting with histones could provide high levels of expression of the anti-tumor substance.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JLE